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CONTENTS

VOLUME TWO SEPTEMBER 1940 NUMBER THREE

BULLETIN OF
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VOLUME 2, 1940

A GENERALIZATION OF CUNNINGHAM'S EXTENSION OF STOKE'S LAW FOR THE FORCE ON A SPHERE

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Cunningham's formula for the force on a sphere moving within a larger concentric spherical boundary is extended to cover a general state of motion of the fluid between them.

Stoke's formula for the force on a sphere moving slowly through a viscous fluid of infinite extent has played an important role in many physical investigations, and has been the subject of much experimental and theoretical study. Various modifications of it have been worked out by different authors; for some account of these see Smoluchowski (1913), Lamb (1924, p. 565-583, 608), and Bulletin of the National Research Council (1931, Chapter 7).

Cunnigham (1910) worked out the force on a sphere moving through a fluid enclosed within a larger concentric sphere, and from this tried to estimate the effect of the presence of many other moving spheres. His results have been used (Heilbrunn, 1928, Chapter 5) in determining the viscosity of a fluid from observation of the rate of motion through it of a large number of particles under the action of applied forces or thermal agitation. For a discussion of Cunningham's work and the many sphere problem see Smoluchowski (1913).

Cunningham found the force on the inner sphere under the assumption that the fluid is at rest* over the surface of the outer sphere, and then considered various sizes for the larger sphere to somewhat correspond to the presence of other particles. Since there is in such a situation no surrounding sphere where the fluid is at rest, and since it is quite easy to remove the assumption of an exactly specified flow at either sphere, it may be worth while to note the general result. This will also be of use in other connections.

I

The complete solution of the equations of slow, potential force motion of an incompressible fluid is given by Lamb (p. 562-564) in a form adapted to a region with concentric spherical boundaries. In

* Williams (1915) treated the same concentric sphere problem by a different method. We shall here more nearly follow Cunningham. Williams gives some diagrams showing flow patterns, both theoretical and observed.

such a motion the mean pressure p of the fluid is a harmonic function and may thus be written as

$$p = \Sigma\, p_n \tag{1}$$

where p_n is a solid harmonic of degree n. The summation is over n and over the various independent solid harmonics (there are $2n + 1$ of these of positive degree n or of negative degree $-n - 1$) of each degree. The fluid motion cannot give rise to a pressure term of degree -1, so that p_{-1} is always zero. Denoting by u, v, w the component velocities of the fluid along the (x, y, z)-axes respectively we have

$$u = \frac{1}{\eta}\Sigma\left\{\frac{r^2}{2(2n+1)}\frac{\partial p_n}{\partial x} + \frac{n\, r^{2n+3}}{(n+1)(2n+1)(2n+3)}\frac{\partial}{\partial x}\frac{p_n}{r^{2n+1}}\right\} \tag{2}$$

$$+\Sigma\left\{\frac{\partial \phi_n}{\partial x} + z\frac{\partial \chi_n}{\partial y} - y\frac{\partial \chi_n}{\partial z}\right\},$$

with the corresponding expressions for v and w obtained by cyclical interchange of x, y, and z. Here η is the coefficient of viscosity of the fluid, while ϕ_n and χ_n are arbitrary solid harmonics of degree n.

The stress exerted in the x-direction across a spherical surface of radius r by the fluid outside the sphere is p_{rx}, where

$$rp_{rx} = \Sigma\left\{\frac{n-1}{2n-1}r^2\frac{\partial p_n}{\partial x} + \frac{2n^2+4n+3}{(n+1)(2n+1)(2n+3)}r^{2n+3}\frac{\partial}{\partial x}\frac{p_n}{r^{2n+1}}\right\} \tag{3}$$

$$+\eta\Sigma\,(n-1)\left\{2\frac{\partial \phi_n}{\partial x} - z\frac{\partial \chi_n}{\partial y} + y\frac{\partial \chi_n}{\partial z}\right\}.$$

The corresponding expressions for rp_{ry} and rp_{rz} are obtained by cyclical interchange of x, y and z. The total force exerted on the sphere in the x direction is given by the integral over the sphere surface

$$F = \int\int p_{rx}\, ds\,. \tag{4}$$

It is evident from the orthogonality properties of surface harmonics that only those in (3) of zero order survive the integration, and further consideration shows that all of these drop out except the term $E\,x/r^3$ in p_{-2}. The final result is

$$F = -4\pi E\,, \tag{5}$$

so that *in any such fluid motion the total* x*-force on a sphere depends only on the coefficient of* x/r^3 *in the expansion of the pressure field in solid harmonics about the center of the sphere as origin.* Similarly, the total y-force on the sphere depends only upon the coefficient of y/r^3, and the z-force only upon that of the z/r^3 term.

II

Such a fluid motion as considered above is uniquely determined throughout a region by its velocity components over the boundary (Lamb, p. 584). We proceed now to determine the value of E in terms of the boundary velocities on two concentric spherical surfaces of radii t and T.

To this end we consider the quantity l defined by

$$l = xu + yv + zw, \tag{6}$$

which is simply r times the outward radial velocity of the fluid. In terms of the above quantities its value (Lamb, p. 564) is

$$l = \frac{1}{\eta}\Sigma \frac{nr^2}{2(2n+3)} p_n + \Sigma n \phi_n . \tag{7}$$

In this expression E appears only in connection with the first order surface harmonic x/r. The following quantities are thus involved with E in the boundary conditions on l;

$$\begin{aligned} p_1 &: \quad Ax \\ p_{-2} &: \quad Ex/r^3 \\ \phi_1 &: \quad Hx \\ \phi_{-2} &: \quad Gx/r^3 \end{aligned} \tag{8}$$

Upon equating coefficients of the x/r surface harmonic we obtain

$$\begin{aligned} \frac{A}{10\eta} t^2 + \frac{E}{\eta}\frac{1}{t} + H - 2G\frac{1}{t^3} &= l_t \\ \frac{A}{10\eta} T^2 + \frac{E}{\eta}\frac{1}{T} + H - 2G\frac{1}{T^3} &= l_T , \end{aligned} \tag{9}$$

where

$$l_r = \frac{3}{4\pi r^4} \int\int xlds \tag{10}$$

is $1/r$ times the coefficient of x/r in the expansion of l in surface harmonics on a sphere of radius r. It is the average over the sphere surface of 3 times the x component of the outward radial velocity of the fluid.

Similarly, considering the boundary values of the velocity component u and picking out the terms involving zero order surface har-

monics gives

$$\frac{A}{6\eta}t^2+\frac{2E}{3\eta}\frac{1}{t}+H=u_t$$
$$\frac{A}{6\eta}T^2+\frac{2E}{3\eta}\frac{1}{T}+H=u_T\ , \tag{11}$$

where

$$u_r=\frac{1}{4\pi r^2}\int\int u ds \tag{12}$$

is the coefficient of the zero order surface harmonic in the expansion of u over a sphere of radius r. It is the average over the sphere surface of the x-component of the fluid velocity.

Solving from (9) and (11)

$$E=3\eta t\frac{2T(T^5-t^5)\,\Delta u-5T(T^2-t^2)(\Delta_1 u-\Delta l)}{5Tt(T^2-t^2)^2-4(T-t)(T^5-t^5)} \tag{13}$$

where

$$\begin{aligned}\Delta u&=u_T-u_t\\ \Delta_1 u&=T^3u_T-t^3u_t\\ \Delta l&=T^3l_T-t^3l_t\ .\end{aligned} \tag{14}$$

Thus *the* x *force on a sphere due to any such fluid motion is expressed in terms of the quantities* (10) *and* (12) *which are certain averages of the fluid velocities over the surfaces of two concentric spheres.* If $v=w=0$ on these surfaces, while u assumes constant values, then $\Delta_1 u=\Delta l$ and the result as expressed by (5) and (13) reduces to that of Cunningham; if then T is made much larger than t it goes over into Stoke's formula.

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PHYSICOMATHEMATICAL ASPECTS OF SOME PROBLEMS OF ORGANIC FORM

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In connection with previous mathematical studies on cell polarity, the possible application of the results obtained before to different embryological phenomena is discussed. Methods for a quantitative mathematical approach to such phenomena as gastrulation, formation of different folds, closing of a half blastula, etc. are outlined.

Of all the problems of biology, the problem of form and structure of multicellular organisms seems to be the most difficult from the point of view of a physicomathematical approach. Even the highly complex phenomena observed in the functioning of the central nervous system and covering the fields of neurophysiology and psychology, have recently been brought within the scope of mathematical treatment (Rashevsky, 1938, 1940a; Landahl 1938, 1939 a, b, 1940; Householder 1938, 1939, 1940). In spite of the amazing progress of experimental embryology and a discovery of a very large number of important and entirely new facts, the complexity of this field seems to increase with increasing study. The quantitative element is still almost completely lacking in the experimental researches, and this seems to be due not so much to a lack of efforts on the part of the experimenter to introduce quantitative measurements, as to the elusive character of the phenomena studied, which makes it almost impossible to point out where and how any quantitative method can be applied and what actually can be exactly measured.

Under such conditions an attempt to present a completed and systematic theory of these phenomena would naturally be premature. But like in all branches of theoretical science, the theory of a group of phenomena must of necessity be preceded by a number of preliminary, abstract theoretical studies, which deal with general conceivable explanations of the phenomena and study a large number of possible explanations, although only one of these possible cases will perhaps be eventually applied (Rashevsky 1938 a, b; 1940 a). In this early stage any theory is of necessity incomplete and fragmentary, the fragments being rather disconnected. But even so, such a theory may at least suggest, where to look experimentally for quantitative rela-

tions, though it may not as yet give any consistent and adequate explanation of known phenomena. This paper is a contribution to such an early stage of the theory of organic form, and the reader is therefore specially requested to keep in mind the above mentioned limitations.

I

In two previous papers (Rashevsky 1940 b, d), we have shown how under relatively simple conditions a cell may possess an automatically regulated axial polarity. This polarity is still of a very simple type of symmetry, much too simple to be applied to any real cases. Nevertheless it possesses some interesting properties, one of them being that when such a cell is in any way divided in two parts, each part restores the same type of polarity, which is possessed by the original cell, regardless of the way in which the division is made. This latter statement however requires a qualification which, while limiting it to some extent, yet opens at the same time some interesting possibilities.

The polarity, which consists in an axial gradient of concentration of a metabolite from pole to pole, may be conveniently measured by the difference x^* of the average concentrations in the two hemispheres. This difference is given (Rashevsky 1940 b) by the approximate expression:

$$x^* = \frac{2}{\alpha}\sqrt{\frac{3(A\alpha an - 1)}{A\alpha an}} . \tag{1}$$

The symbols α, a and n have the same meaning as in the preceding paper. As regards the constant A, it has two different expressions, depending on the type of metabolic reaction considered. If we consider the case of a cell producing a substance, which diffuses outward, then (Rashevsky 1940 b):

$$A = \frac{r_0^2(2D + r_0 h)}{3D(2D + 3r_0 h)} , \tag{2}$$

the notations being again the same as before. If on the other hand we consider the case of a substance, which is produced in one part of the cell and consumed in another part, and does not leave the cell at all, then (Rashevsky, 1940 d):

$$A = \frac{r_0^2}{r_0^2 b + 3D} \tag{3}$$

b being a reaction constant, defined in the previous paper.

The variation of A with radius r_0 of the cell is quite different for the two cases. In the case represented by equation (2) A increases from zero to infinity, varying for large values of r_0 like r_0^2. In the second case, represented by equation (3), A tends to an assymptotic value $1/b$. For such values of r_0, for which $r_0^2 b >> 3D$, or $r_0^2 >> 3D/b$, the quantity A is practically constant. Taking $b \sim 10^{-2}$ sec^{-2} and $D \sim 10^{-7}$ cm^2 sec^{-1}, we find that A will be approximately constant for $r_0 > 10^{-2}$ cm.

Let us first consider the case corresponding to equation (3), assuming that r_0 is within such a range as to make A approximately constant. Let us now divide the cell into halves equatorially. For each half the quantity x^* will again be determined by equation (1). But while the quantity A remains the same, n has now changed, being different in the two halves. For n denotes the *average* concentration of the catalyst in the cell, and according to the discussion of the two preceding papers (Rashevsky 1940 b, d), that concentration is different in the two hemispheres. In the notations of the previous paper, the concentrations in the two hemispheres are n_1 and n_2, and the difference $n_2 - n_1$ is given by equation (23) of *loc. cit.* (Rashevsky 1940 b). On the other hand, x is given by equation (27) of the same paper. It follows therefore, since x^* is the root of that equation (27), that

$$n_2 - n_1 = \frac{x^*}{Aa} . \tag{4}$$

Combining equation (1) and (4) we have:

$$n_2 - n_1 = 2\sqrt{\frac{3(Aa\alpha n - 1)}{A^3 a^3 \alpha^3 n}} . \tag{5}$$

On the other hand we have (Rashevsky 1940 b):

$$n_1 + n_2 = 2n . \tag{6}$$

Equations (5) and (6) give:

$$n_1 = n - \sqrt{\frac{3(Aa\alpha n - 1)}{A^3 a^3 \alpha^3 n}} \tag{7}$$

and

$$n_2 = n + \sqrt{\frac{3(Aa\alpha n - 1)}{A^3 a^3 \alpha^3 n}} . \tag{8}$$

When we divide the original cell equatorially into halves then, while in each half x^* is given by equation (1), yet the role of n in

one half is taken over by $n_1 < n$ and in the other by $n_2 > n$. Since, by the nature of its derivation, equation (1) holds only for $Aa\alpha n > 1$, and at the same time when $Aa\alpha n$ is only *very slightly* greater than one, an increase in n results in an increase of x^*. Hence, of the two half cells, the one that corresponds to pole N^0 2 of the original cell will have a quantitatively larger polarity than the one corresponding to pole N^0 1.

As regards the half cell corresponding to pole N^0 1, it can be shown, that with the particular mechanism of polarity adopted here, and leading to equation (1), it will loose its polarity after the division, for n_1 will decrease to such an extent that $Aa\alpha n_1$ will become always less than 1. A somewhat different, more complicated mechanism which shall be described in a separate paper, can however be conceived, in which this limitation does not hold, and in which both halves preserve their polarity. In one half however the polarity is enhanced, in the other weakened.

A further division of each half cell again in an equatorial plane will result in four quarter cells, in which the polarity will increase from one extreme cell to the other. Thus if an originally polar cell is divided by a series of equatorial sections into a group of smaller cells, the polarity in the cells of the group originating from pole N^0 1 decreases, that in the other cells — increases. But as n decreases more and more in one half of the cells, a situation will be reached when $Aa\alpha n < 1$. From now on the cells for which this situation obtains loose their polarity entirely, while the polarity of the other cells increases. If, as in the segmentation of an egg, the division into daughter-cells is not accompanied by any appreciable growth, the daughter cells will become smaller and smaller, until finally their radii r_{0i} become so small that $r_{0i} < 3D/b$. In that case A begins to decrease. The decrease of A enhances the decrease of x^* in the cells originating from hemisphere N^0 1, and slows down the increase of x^* in the cells, originating from the hemisphere N^0 2. As r_{0i}, and therefore A, tends to zero, $Aa\alpha n - 1$ decreases more and more and thus x^* will reach a maximum and then decrease.

We now have the following situation. If an originally polar cell is divided into a few parts, each part preserves the same qualitative polarity, although *quantitatively* the parts will be different. As the segmentation proceeds, a process of *differentiation* takes place in the aggregate of cells. At one pole of the aggregate the cells gradually *loose* their polarity, while at the other pole the polarity of the cells increases, and if as a result of segmentation, the individual cell becomes sufficiently small, it reaches a maximum and begins to decrease. An equatorial section of such an aggregate in two, at the proper stage,

results now in two qualitatively different halves: one polar, the other non-polar.

While this picture is highly oversimplified, it offers nevertheless a model of a phenomena commonly found in embryology. Moreover it gives us a quantitative picture of what happens.

Quantitatively the change of the average n for each division is given by the non-linear difference equations:

$$n'_i = n'_{i-1} - \sqrt{\frac{3(A_{i-1}a\alpha n'_{i-1} - 1)}{A^3{}_{i-1}a^3\alpha^3 n'_{i-1}}} \tag{9}$$

for the pole N° 1 , and

$$n''_i = n''_{i-1} + \sqrt{\frac{3(A_{i-1}a\alpha n''_{i-1} - 1)}{A^3{}_{i-1}a^3\alpha^3 n''_{i-1}}} \tag{10}$$

for pole N° 2. For the case of equal division the value A_i is defined by

$$A_i = \frac{(0.8)^{2i} r_0^2}{(0.8)^{2i} br_0^2 + 3D} ; \tag{11}$$

where r_0 is the initial radius. The corresponding values of x^* are then obtained from equation 1 into which the values of n'_i or n''_i and of A_i are substituted. If the rate of segmentation is given as a function of time, then i is also a function of time, $i = f(t)$, and the whole process of differentiation is described quantitatively in its dependence on time. A direct measurement of the polarity as defined here may be impossible. But by studying different theoretical cases of the influence of polarity on other properties of the cell, as we shall do in the subsequent sections, we may derive relations between directly observable quantities. But even these considerations suggest the measurements of some quantities which may be used as a natural measure of polarity.

A more complex situation may also be considered, by assuming that the quantity of catalyst in the system does not remain constant, but varies with respect to time according to some definite law, expressed by a differential equation governing the kinetics of the reaction responsible for its production or destruction.

II

In a previous paper (Rashevsky 1940 c) we have seen how under the influence of different forces, the cells of an aggregate, formed by the segmentation of a single egg, may arrange themselves in the shape of a hollow spherical shell. Combining these results with the considerations of the preceding section we find that in such a shell

the cells in the neighborhood of one pole will be relatively strongly polarized, whereas in the other part of the shell they will not be polarized at all (Figure 1). This results in an asymmetry of the physical

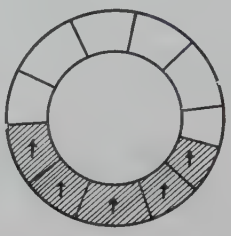

FIGURE 1

properties of the shell, and it is of interest to study possible effects of such an asymmetry. To this end we must consider what effects a polarity of the nature discussed here may have on other properties of a cell. Of the many possibilities we shall consider here only three.

a). The difference of physicochemical properties due to the differences of concentrations at the two poles may result, among other things in a differential growth of the cell at the two poles. Consider for simplicity a plane disc composed of one layer of cells, polarized in the direction normal to the disc (Figure 2). If due to the polariza-

FIGURE 2

tion the upper surface of the disc grows more rapidly, than the lower one, then the disc will bend, becoming convex upwards. Let the original diameter of the disc be equal to S. Let due to differential growth, the diameter of the lower surface become S_1 and that of the upper surface $S_2 > S_1$. Let $S_2 - S_1 = \delta$ and denote the thickness of the disc by Δ. Considering that the difference in growth rate is the same for all cells of the disc, we shall find that it will assume a shape of a spherical sector. Denoting by ϕ the angle which is subtended by such

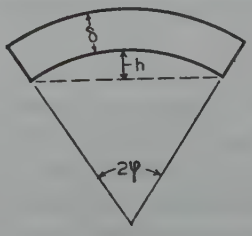

FIGURE 3

a bent disc from its center of curvature and by r the radius of curvature of the lower surface, we have (Figure 3):

$$\delta = \phi \Delta \,, \tag{12}$$

and

$$h = r\left(1 - \cos\frac{\phi}{2}\right) . \tag{13}$$

Furthermore we have

$$r = \frac{S_1}{\phi} . \tag{14}$$

Substituting the value of ϕ from equation (12) into equation (13) and (14) and substituting the value of r from equation (14) into equation (13) we find:

$$h = \frac{S_1 \Delta}{\delta}\left(1 - \cos\frac{\delta}{2\Delta}\right) . \tag{15}$$

If we now have the rate of growth of both surfaces given as functions of the polarization x^* and if the latter is itself prescribed as a function of time by consideration of the preceding section, then S_1, d and δ are known functions of time, and equation (15) gives us b, the "depth" of the buckling disc as a function of time.

As an *illustration* consider the case that

$$\frac{dS_1}{dt} = a_1 x^* \;; \qquad \frac{dS_2}{dt} = a_2 x^* \;; \tag{16}$$

$$a_2 - a_1 = a > 0 \,,$$

while Δ remains constant.

Then, if

$$x^* = u(t) \tag{17}$$

we have

$$\begin{aligned} S_1 &= S + a_1 \textstyle\int_0^t u(t)\,dt = S + a_1 U(t) \;; \\ S_2 &= S + a_2 \textstyle\int_0^t u(t)\,dt = S + a_2 U(t) \;; \\ \delta &= aU(t) \,. \end{aligned} \tag{18}$$

Hence, introducing equations (18) into equation (15), we have:

$$h = \frac{[S + a_1 U(t)]\Delta}{aU(t)}\left[1 - \cos\frac{aU(t)}{2\Delta}\right] . \tag{19}$$

As can be readily seen by expanding $\cos(\delta/2\Delta)$, equation (15) gives $h = 0$ for $\delta = 0$. The value of h reaches its maximum in the neigh-

borhood of $\delta/2\Delta = \pi$, which corresponds to $\phi = 2\pi$, or a completely closed shell. For $\delta = 0$ we have $h < 0$, which means a disc convex downward.

If due to the polarization of the cells in the shaded region of Figure 1 the inner side of the cells grows faster than the outer side, that region will buckle inward, and we shall have a phenomenon, reminding of gastrulation. Equation (19) gives us the *depth of the invagination* after it actually started, as a *function of time*. Making different assumptions about the effects of the polarization upon the differential growth rate, we shall have different forms of equation (19), which may be compared to different observed cases.

True enough, the invagination in a gastrula does not proceed actually in such a simple way. But these simple considerations should pave the way for more complex cases. By considering different disturbing factors, such as nonuniform thickness of the blastula, etc., we may arrive at a mathematical expression of more complex forms of invagination, which come closer to the actually observed ones. It must be remarked however, that while for instance in *Amphibia* the process of invagination is very different from the simple scheme here considered, in some cases, like *Arbacia* or *Amphioxus,* it is, while still complex, to some extent comparable with our oversimplified picture. In any case the importance of having the phenomenon of invagination properly *timed,* describing the depth of invagination quantitatively as a function of time, becomes apparent. Hitherto no observations of that kind have been made. In order to obtain smooth results, it will probably be necessary to use a very large number of observations, and take averages, due to individual variations. But in principle here is a definite quantitative problem of embryology, which awaits a quantitatively minded embryologist to tackle it experimentally.

That actual gastrulation is probably due to some such process as above discussed, seems to be made rather probable both by the model experiments of J. Speck (1918) as well as by the recent observations on the invagination of the isolated vegetative parts of *Dendraster excentricus* by A. R. Moore and Agnes S. Burt (1939). In a previous paper (Rashevsky 1940 e), we have considered asymmetric distributions of metabolism in a blastula. If the effective rate of metabolism (Rashevsky 1940a) is positive everywhere in the blastula, except in a region near the vegetative pole, then the diffusion forces in that region will be directed inward, and cause that region to invaginate. Taking these forces to be of the usual order of magnitude for diffusion forces (Rashevsky 1940 a), considering that the principal resistance offered to invagination is the flow of the blastocoel liquid

through the invaginating part, as the blastocoel gradually closes, and taking for this resistance a value used previously (Rashevsky, 1938, p. 106), we find for the time necessary for a complete invagination a value of the order of magnitude of 10 hours, which agrees with some observations (Taylor 1937). From this picture one could also derive a relation between depth of invagination and time. Such a mechanism is however made rather unlikely by both the above mentioned experiments of Moore and Burt and by those of J. Brachet (1934). In the former an invagination is observed in open isolated parts of blastula, in which the conditions of a closed metabolizing shell are definitely not satisfied. In the latters, it has been shown that gastrulation may proceed normally in the absence of oxygen. Since oxygen is the only substance with negative rate of metabolism, used by an early embryo in quantities sufficient to produce appreciable forces, Brachets' observations seem to rule out the above possibility. Thus some sort of polarization resulting in an autonomous invagination of the vegetative region, regardless of whether it forms a part of a whole blastula or not, seems to be the cause of gastrulation.

b). We now consider a different possible mode of action of cell polarity.

Referring again to Figure 2 we may consider the case, that due to a difference of concentrations on both sides of the disc, the surface tension on the upper side is smaller than on the lower. This will again result in a convexity upwards. The calculation of the variation of the convexity, with time would proceed as follows. We first calculate the buckling of an elastic disc under the influence of such forces. Then apply the analogy between elastic deformation and plastic flow (Rashevsky, 1938 a, 1940 a).

c). The most interesting consideration however is perhaps one which does not involve any additional assumptions. Considering again Figure 2 and assuming that the polarization is of the type corresponding to equation (3) and is so directed that the concentration is higher at the top surface, than at the bottom, we have a situation represented on Figure 4. If $c_1 > c_2 > c_3$, then, since c plays the role of a po-

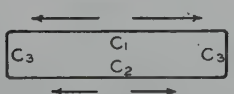

FIGURE 4

tential, the surface forces are distributed as indicated by the arrows. This again results in a buckling upward, the rate of which may be calculated in a similar manner as suggested above (C.f. also section III). In this way we would have an equation for the rate of invagina-

tion, expressing the latter in terms of essentially the same constants, which have been used previously in cell biophysics.

III

If the origin of cell polarity may be considered as being connected with the axial gradients of concentration, then a spherically symmetric cell may be said to have radial polarity. The axial polarity, as studied here is due to the interaction of a metabolite with some catalyst. By considering two or more independent metabolites of which one behaves in such a way as to produce an axial polarity, while the other has an approximately spherical distribution, we obtain a cell in which a radial polarity is superimposed upon an axial one (Figure 5).

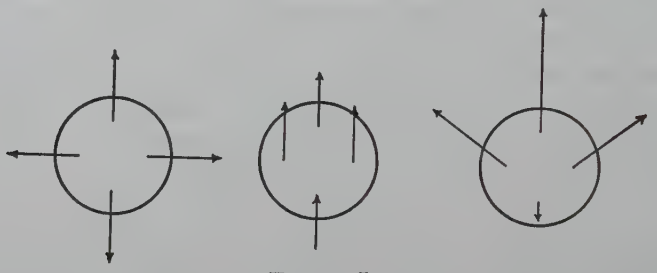

FIGURE 5

In fact such a superposition may occur even in case of a single metabolite. In the case studied before (Rashevsky 1940 b) which corresponds to equation 2, the concentration of the metabolite is smaller at the periphery than near the center, only the maximum of concentration lies excentrically, giving thus an axial polarity.

As a result of the segmentation of such a cell, we shall have a blastula, which also exhibits the mixed polarity. If we consider the radial component and its effects, we see that by a similar argument as used before, we may make the radial component responsible for the *closing of a half blastula,* obtained by cutting a whole blastula in two. By similar reasonings as before we may obtain an equation giving us the rate of closure and its dependence on the initial conditions, that is on whether we observe a half blastula or a smaller or larger fraction of it. The phenomenon of closure of parts of blastula is well known (Horstadius, 1939; Weiss 1939). However only qualitative descriptions of the phenomenon are available. Quantitative observations, which in this case would not be so difficult at all, would give us valuable information as to the mechanism responsible for the closure, for different mechanisms will lead to different relations for the decrease of the opening with respect to time.

Compared with the problem of invagination, the problem of clos-

ing of a part blastula presents an additional interesting feature. Consider a partly closed blastula (Figure 6), whose cells do not possess

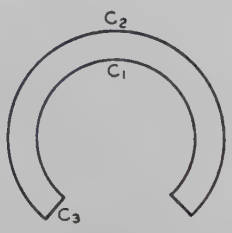

FIGURE 6

any intrinsic polarity and into which a substance diffuses *from outside*. As can be readily seen from general physical considerations and proven by the application of the usual approximation method, when the external diffusion coefficient D_e is finite the concentration c_1 at the inner surface will be smaller than the concentration c_2 at the outer surface, so that $c_1 < c_2$. Thus inside the cellular layer the cells will now show a polarity, but this polarity is so to say an induced one, persisting only as long as the cell is a part of the whole aggregate, having the shape of a non completely closed shell. The polarity will be the smaller, the more "open" the blastula and will vanish completely for a perfectly flat disc. Considering now the effects of *this* polarity either on differential growth or on surface tension or directly upon the diffusion forces, we shall again obtain different expressions for the rate of closure, which may be compared with experiments.

The above discussed "induced" polarity raises another important question, namely: if an intrinsically polarized cell is brought into an external diffusion field, will this field tend to orient the polarity of the cell in a definite direction? If yes, will the forces exerted by the external field upon that cell be such as to orient the whole cell, or such as to change the orientation of polarity within the cell? This problem, which may present some interesting physicomathematical aspects, is of interest in connection with the experiments of implanting additional micromers into *Arbacia* blastulae.

IV

We shall now consider still another possible effect of polarity. Consider now a closed shell of thickness Δ, consisting of several layers of cells (Figure 7). Such a multicellular layer possesses a certain degree of elasticity like any other tissue. Let those cells be polarized radially. Denoting by r_1 and r_2 the inner and the outer radii, by S_1 and S_2 the length of the great circles on the internal and external surfaces and putting $S_2 - S_1 = \delta$, we have

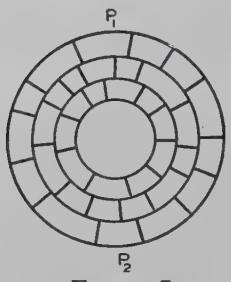

FIGURE 7

$$\Delta = r_2 - r_1 = \frac{S_2 - S_1}{2\pi} = \frac{\delta}{2\pi} . \tag{20}$$

If δ, due to polarity, increases with time, so that $\delta = U(t)$, then the thickness Δ also increases. This results in radial tensions inside of the layer, the average radial stress being given by

$$\sigma_r = E \frac{\Delta - \Delta_0}{\Delta_0} , \tag{21}$$

where E denotes the elasticity modulus of the tissue, and Δ_0 the initial thickness of the shell. We may speak approximately of the tensil strength σ_t of such a tissue. When $\sigma_r > \sigma_t$, the tissue will break in the radial direction and form approximately concentric layers with a space in between. If $\delta = U(t)$, then $\Delta = U(t)/2\pi$, and the time at which the rupture, or speaking in embryological terms, delamination will occur, is given by

$$E \frac{U(t) - 2\pi \Delta_0}{2\pi \Delta_0} = \sigma_t . \tag{22}$$

If an axial polarity is superimposed upon the radial one, so that the radial polarity varies from point to point, being say, largest at the point P_1 (Figure 7), a smallest at P_2, then δ is a function of the position on the surface and may be conveniently described as a function of the angle ϕ (Figure 7). Thus.

$$\delta = U(\phi, t) , \tag{23}$$

and equation (22) now becomes

$$E \frac{U(\phi, t) - 2\pi\Delta_0}{2\pi\Delta_0} = \sigma_t . \tag{24}$$

Solved with respect to t, it gives t as a function of ϕ,

$$t = v(\phi) . \tag{25}$$

Thus now the layer splits into two lamina, gradually beginning with one pole and ending at the other. While the simple picture used here does not correspond to any real situation, yet it does remind of the delamination of mesoderm in Amphibia, and definitely suggests a quantitative study of the process of delamination with respect to time.

The author is indebted to Mr. H. D. Landahl for checking the calculations.

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CONTRIBUTIONS TO THE MATHEMATICAL BIOPHYSICS OF ORGANIC FORM III. DEFORMATION OF SHELL SHAPED CELLULAR AGGREGATES

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The average concentrations of a substance diffusing into or from an open spherical shell, in which it is consumed or produced at a constant rate, are calculated by the approximation method. An application of the result to the problem of deformation of such a shell under the influence of diffusion forces is indicated.

In the preceding paper (Rashevsky 1940) we have indicated the interest of studying the diffusion processes and mechanical forces in cellular aggregates, which have the shape of open spherical shells. In the present paper we shall give as an illustration a very crude treatment of the problem of deformation of such an aggregate.

Consider an open spherical shell, the meridional section of which is represented on Figure 1. Let a substance be metabolized inside the body of the shell at a constant rate q gm $\cdot$ cm^{-3} sec^{-1}. For simplicity we shall consider the permeability h of the surfaces of the shell as infinite. We shall denote by D_i and D_e the internal and external diffusion coefficients respectively. The average concentration inside the shell we shall denote by $\bar{c}$, while c_1, c_2 and c_3 denote the average concentrations at the different surfaces of the shell, as is clear from Figure 1. By c_4 we shall denote the average concentration in the plane of the "opening" or "mouth" of the shell. The remaining notations can be understood from Figure 1. We shall put $r_1 + \delta = r_2$. We assume

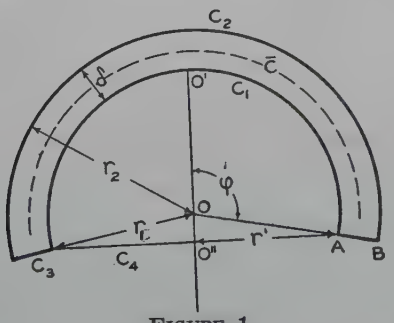

FIGURE 1

$\delta << r_1$, and shall therefore put everywhere $r_1 = r_2 = r$, except when r_1 and r_2 occur as a difference $r_2 - r_1$.

Denoting by S_1 and S_2 the areas of the internal and external surfaces respectively and by S_3 the area of the surface formed by AB; denoting further by V the volume of the shell, we have

$$S_1 = 2\pi r_1^2(1 - \cos\phi)\ ;\quad S_2 = 2\pi r_2^2(1 - \cos\phi)\ ;$$
$$S_3 = 2\pi r'\delta = 2\pi r_1\delta \sin\phi\ ;\quad r' = r_1 \sin\phi\ ; \tag{1}$$
$$S_4 = \pi r'^2 = \pi r_1^2 \sin^2\phi\ ;\quad V = 2\pi r^2(1 - \cos\phi)\delta\ .$$

The concentration c inside the shell has its average value $\bar{c}$ somewhere between the dotted line and each surface, so that the average gradients inward and outward are of the order of $4(\bar{c} - c_1)/\delta$ and $4(\bar{c} - c_2)/\delta$. From physical considerations it can be seen, that the gradient near the opening and in the direction of increasing angle ϕ is of the order $4(\bar{c} - c_3)/\delta$. Considering as before that outside of the shell the gradient extends over a region of the order of r, we now have the following equations for the material balance:

$$4D_i\frac{\bar{c} - c_2}{\delta} = D_e\frac{c_2 - c_0}{r}\ ;\qquad 4D_i\frac{\bar{c} - c_3}{\delta} = D_e\frac{c_3 - c_0}{r}\ . \tag{2}$$

Moreover we have a flow inside the shell, due to the fact, that c_1 is different from c_4. The average distance $\bar{\delta}$ over which the difference $c_1 - c_4$ extends is of the order of $\frac{1}{2}\,O'\,O''$ (Figure 1), hence

$$\bar{\delta} = \frac{r}{2}(1 - \cos\phi)\ . \tag{3}$$

Hence

$$4D_i\frac{\bar{c} - c_1}{\delta} = 2D_e\frac{c_1 - c_4}{r(1 - \cos\phi)}\ . \tag{4}$$

Moreover the total flow through the surface S_1 equals the total flow through the surface S_4. Hence

$$2D_eS_1\frac{c_1 - c_4}{r(1 - \cos\phi)} = D_eS_4\frac{c_4 - c_0}{r}\ . \tag{5}$$

Finally we have the equation expressing the equality of the amount metabolized with that flowing out:

$$r\,\delta(1 - \cos\phi)\,q = 4D_i\frac{\bar{c} - c_1}{\delta}r(1 - \cos\phi) + 4D_i\frac{\bar{c} - c_2}{\delta}$$
$$\times r(1 - \cos\phi) + 4D_i(\bar{c} - c_3)\sin\phi\ . \tag{6}$$

From equations (2), (4), (5) and (6) we can determine the quantities $\bar{c}$, c_1, c_2, c_3, c_4 by elementary, though somewhat cumbersome calculations. Putting

$$\sin \phi = s_1 ; \quad 1 - \cos \phi = s_2 , \tag{7}$$

we find

$$\bar{c} = c_0 + \frac{\delta s_2 q r}{4 D_i D_e} \frac{(4 D_i r + D_e \delta)(8 D_i r s_2 + 2 D_i r s_1^2 s_2 + D_e \delta s_1^2)}{(8 D_i r s_2 + 2 D_i r s^2{}_1 s_2 + D_e \delta s^2{}_1)(r s_2 + \delta s_1) + (4 D_i r + D_e \delta) r s_1^2 s_2} \tag{8}$$

When $q > 0$, then $\bar{c} - c_0 > 0$, as should be the case. For $\phi = \pi$, $s_1 = 0$, $s_2 = 2$, the shell becomes closed. Then

$$\bar{c} = c_0 + \frac{\delta^2 q}{4 D_i} + \frac{\delta r q}{D_e} , \tag{9}$$

an equation, that can be obtained directly.

We shall be interested in the quantity $c_2 - c_1$; this is given by

$$c_2 - c_1 = \frac{2 D_i D_e r \delta (2 s_1^2 - 4 s_2 - s_1^2 s_2)(\bar{c} - c_0)}{(4 D_i r + D_e \delta)(8 D_i r s_2 + 2 D_i r s_1^2 s_2 + D_e \delta s_1^2)} . \tag{10}$$

It can be shown that the expression $(2 s_1^2 - 4 s_2 - s_1^2 s_2)$ is always negative. Therefore when $\bar{c} - c_0 < 0$, $c_2 - c_1 > 0$, or when $q < 0$, then $c_2 - c_1 > 0$.

For $q < 0$ the shell is subject to an inwardly directed pressure of the order of magnitude of

$$p = \frac{RT}{M}(c_2 - c_1) . \tag{11}$$

which tends to close the shell. To find the equation governing the process of such a closure, we consider the corresponding elastic problem. An elastic shell of thickness δ, subject to a uniform pressure p is deformed so that the radius r' of the opening changes by an amount given by (Hetenyi 1939):

$$\frac{\Delta r'}{r'} = \frac{p r}{2 E \delta}(1 - \mu) ; \tag{12}$$

where E is the elasticity coefficient, and μ the Poisson's ratio.

Consider the shell composed of cells as being a plastic body of an average viscosity η (which is not to be confused with the viscosity of protoplasm of the cells composing the shell), we find (Young 1939) the differential equation for the variation of r' with respect to time by

putting in equation (12) $\mu = 1/2$, $E = \eta$, and substituting dr'/dt for $\Delta r'$. This gives:

$$\frac{1}{r'}\frac{dr'}{dt} = -\frac{pr}{4\delta\eta}. \tag{13}$$

By means of the fourth and sixth of the relations (1), we may express r' and $r(=r_1=r_2)$ in terms of ϕ and V. Considering δ as constant during the deformation, we thus have a differential equation for the variation of ϕ. Such an equation could be compared with the rate of closure of a half blastula, if quantitative data were available.

The author is indebted to H. D. Landahl for checking the calculations.

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ON THE FORMAL THEORY OF NERVE CONDUCTION

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A general solution of the formal nerve conduction problem is given. As illustrations of the general method, the capacitative single-factor and the non-capacitative Lapicque problems are solved. Comparisons between velocity formulae for capacitative and non-capacitative models indicate that previously determined non-capacitative velocities are considerably too high.

The formal theories of nerve conduction as presented by N. Rashevsky (1938, part II) and W. A. H. Rushton (1937) have usually included the simplifying assumption that the network representing the nerve axon is non-capacitative. An attempt to extend one of Rashevsky's theories to include capacitative effects has been made (Weinberg, 1939) but was rather unsuccessful, primarily because the problem was treated from the integral instead of differential standpoint.

In the present paper a general solution will be outlined for all Rashevsky-type formal nerve conduction problems; in principle, by the use of this method the steady state velocity of conduction can be calculated for any generalized capacitative nerve network in which excitation is governed by any one of the formal excitation theories (Rashevsky, 1938, part II). As an illustration of this method, the velocity of conduction will be calculated for some simplified models among which may be found all those considered by previous writers.

General Equations. The formal nerve conduction problem is divided into two separate parts: first, on the basis of some assumed electrical structure the distribution of currents in the nerve is calculated; and second, the currents so calculated are introduced into an excitation equation which describes the time variation of excitatory state as a function of the stimulating current. From the condition that excitation occurs when the excitatory factor exceeds a threshold, the velocity of propagation may be calculated.

Suppose that some general electrical network has been assumed to represent the nerve, and suppose the steady state has been reached. Then the differential equation satisfied by the local bio-electric current, I, will be of the form

$$F(d^n I/d\xi^n,\ d^{n-1} I/d\xi^{n-1}, \cdots I) = 0\,, \tag{1}$$

where $\xi = x - vt$ measures the distance x from an origin moving with the disturbance whose velocity is v; equation (1) is obtained from Kirchhoff's laws in the usual manner (Webster, p. 44). The solution of equation (1) is

$$I = \phi(\xi) \; ; \tag{2}$$

whether this solution can actually be calculated in closed form depends, of course, on F — that is, on the the electrical character of the assumed network.

The excitation equation governing the variation of an excitation factor y, will in general be a differential equation of the form

$$f(d^n y/dt^n, d^{n-1}y/dt^{n-1} \cdots y, \; d^n I/dt^n, \; d^{n-1}I/dt^{n-1} \cdots I) = 0 \tag{3}$$

which may be solved for I as a function of y and the derivatives of y and I:

$$I = \psi(y, dy/dt, \cdots dI/dt, \; d^2I/dt^2 \cdots), \tag{4}$$

or, in the steady state, since $d/dt = -v(d/d\xi)$,

$$I = \psi(y, -vdy/d\xi, \; \cdots \; -vdI/d\xi, \; v^2d^2I/d\xi^2 \cdots). \tag{5}$$

The derivatives of I can be calculated from equation (2), and if they are substituted into (5), ψ becomes a function of y, ξ, and v alone. Upon equating the two expressions for I given in equations (2) and (5), one obtains

$$\phi(\xi) = \psi(y, -vdy/d\xi, \; v^2d^2y/d\xi^2 \cdots), \tag{6}$$

which is a differential equation in y with solution $y = y(\xi, v)$. The steady state velocity is then determined from the condition that at $\xi = 0$ (i.e., $x = vt$), y must just reach the threshold value y_0:

$$y_0 = y(0, v). \tag{7}$$

Equation (7) is an algebraic or transcendental equation in v which has the solution

$$v = v(y_0) \tag{8}$$

and this velocity formula may be expressed in terms of the rheobase since y_0 is related to the rheobase in a known manner. The method just outlined is similar in character to that used by Rushton (1937) and Umrath (1928); it is much simpler than the functional equation solution of Rashevsky.

Applications: As an illustration of the preceding general considerations, the velocity formula (or rather the algebraic equation (7) determining the velocity) for a capacitative nerve model obeying

a general two factor excitation law will be derived. A very simple capacitative model, shown in the accompanying figure, will be assumed to represent the nerve. The capacitances C may be identified with the capacitance of the nerve membrane, ρ with the transverse leak resistance of the membrane, r_i and r_e with the interior and exterior longitudinal resistances, and E with the action voltage, all line constants being measured per unit length. In the present formal model, E is assumed to be zero until action occurs, at which time E suddenly attains a steady value E_0. *

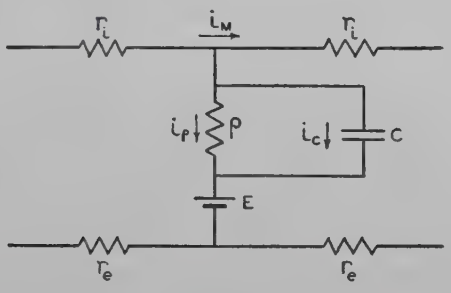

FIGURE 1

Before writing down the differential equation of this circuit, it will be well to consider which of the network currents — i_ρ the current through the transverse resistance ρ, i_e the current into the condenser, or i_M the longitudinal current — should be identified with the exciting current of equation (3). Fortunately, this question does not present any difficulty, for in the steady state, as may be easily verified, all three currents are proportional. For this reason, any linear combination of these currents may be used to represent the exciting current, the only effect on the excitation equation being to change the numerical value of the constants in it, without changing the form of the function f of equation (3). Inasmuch as the numerical values of these constants are obtained only from experiments in which the exciting current is the external stimulating current (Blair, 1932), the values of the constants to be assigned for re-excitation by action currents are not directly determinable, and these values are not significant for the present.

* The general argument given here remains essentially unaltered if a non-explosive change in E is assumed to occur, so that in the steady state E would be some continuous function of ξ, say $E(\xi)$. This function would be closely related to the observed action potential spike. The differential equation for steady state conduction would now be continuous throughout the ξ range, but it could not be integrated, in general, except by numerical methods. This type of non-explosive change has been discussed elsewhere (Offner, Weinberg, and Young 1940). The assumption that E remains at E_0 even after the impulse has passed does not affect the velocity appreciably, as is shown in the previously mentioned paper.

If i_ρ is identified with the local exciting current, then the differential equation for i_ρ may easily be shown to be

$$\rho\partial^2 i/\partial x^2 - M\rho C\,\partial i/\partial t - Mi + \partial^2 E/\partial x^2 = 0 \tag{9}$$

where $M = r_i + r_e$, and the subscript ρ has been dropped from i_ρ. In the steady state, since $\partial/\partial t = -v\partial/\partial\xi$, $\partial/\partial x = \partial/\partial\xi$, this equation becomes

$$\rho d^2 i/d\xi^2 + vM\rho C\, di/d\xi - Mi + d^2E/d\xi^2 = 0 \tag{10}$$

the solution of which is (Rushton, 1937 p. 216)

$$i = i_0\, e^{-\xi/L'} \tag{11}$$

where i_0 is the action current through ρ at the junction of excited and unexcited regions, $1/L' = [(MCv/2)^2 + 1/L^2]^{\frac{1}{2}} + MCv/2$, and $L = \sqrt{\rho/M}$, the characteristic length.

The most general two-factor excitation theory may be formulated as a second order differential equation

$$d^2y/dt^2 + \alpha dy/dt + \beta y = a di/dt + bi \tag{12}$$

where y is the difference between excitatory and inhibitory ("accommodation") factors and so measures the state of excitation of the nerve. Equation (12) is simply one way of writing the two first order equations of the Hill-Rashevsky excitation theory (Hill, 1936; Rashevsky, 1938, chap. 21); if $b = 0$, the equation reduces to the "normal accommodation" case of the Hill-Rashevsky theory which is equivalent to the Monnier theory (1934). The constants α, β, a and b are easily expressed in terms of the constants of the original theories; however, for the present, it is sufficient to note that a and α are related to the rheobase, R, by $R = \alpha y_0/a$, where y_0 is the excitation threshold.

Equation (12) may be written in the form

$$i = (1/a)\int_0^t (d^2y/dt^2 + \alpha dy/dt + \beta y - bi)\,dt \tag{13}$$

as in equation (4); equating the two expressions for i from (11) and (13) and differentiating one obtains (for the steady state where $d/dt = -vd/d\xi$)

$$d^2y/d\xi^2 - (\alpha/v)\,dy/d\xi + \beta y/v^2 = (a/vL' + b/v^2)\,i_0\, e^{-\xi/L'}. \tag{14}$$

The solution of this equation is readily seen to be

$$y = \frac{(aL'v + bL'^2)\,i_0 e^{-\xi/L'}}{v^2 + \alpha L'v + \beta L'^2}. \tag{15}$$

Since at the junction between the two regions $\xi = 0$ and $y = y_0$ the algebraic equation defining the velocity [equation (7) of the previous section] is found from (15):

$$\frac{v^2}{L'^2} + (\alpha - \frac{ai_0}{y_0})\frac{v}{L'} + \beta - \frac{bi_0}{y_0} = 0 . \qquad (16)$$

Equation (16) involves high powers of v (since L' is a function of v), and so it cannot be solved exactly, although numerical solutions are feasible. Certain simplifying assumptions can be made which will lead to equations which are more easily handled, and these will be considered now.

Capacitative Networks. The simplifications which can be introduced into the theory are of two sorts: on the one hand, the electrical network can be simplified by, say, eliminating the capacitative elements, and, on the other hand, the general excitation equations can be simplified in various ways. If the capacitative network is used, (16) is the fundamental equation defining the velocity for the general two-factor excitation theory. The various simplifications introduced into (16) by using simpler excitation theories may be listed as follows:

1. "Normal" accommodation: $b = 0$.
2. Lapicque theory (Lapicque, 1926 p. 184; Rashevsky, 1931): $\beta = 0$, $b \neq 0$.
3. Single-factor, Blair (1932) theory: $\beta = b = 0$.

Case 3 is the one studied previously by the writer (Weinberg, 1939); the asymptotic velocity for this case can now be calculated. Upon setting $\beta = b = 0$ in (16) and using the expression for the rheobase $R = \alpha y_0/a$, one finds the velocity to be

$$v = \alpha L' \lambda \qquad (17)$$

where $\lambda = (i_0 - R)/R$ is the "safety factor." Equation (17) may be solved for v:

$$v = \frac{\alpha \lambda L}{\sqrt{1 + \alpha\lambda MCL^2}} . \qquad (18)$$

If, as Rushton (1937) assumes, $\alpha = 1/C\rho$, then equation (18) may be written as

$$v = \frac{\lambda}{C\sqrt{M\rho(1+\lambda)}} \qquad (18A)$$

Non-Capacitative Networks. To illustrate further the power and generality of the present method, the results for a non-capacitative

network will also be considered briefly. For a non-capacitative network $L' = L$, so that from (16) the general velocity equation is

$$\frac{v^2}{L} - \alpha\lambda\frac{v}{L} + \beta - \frac{bi_0}{y_0} = 0 , \tag{19}$$

which has the two positive solutions *

$$v = (\frac{\alpha\lambda L}{2}) \pm \sqrt{(\alpha L\lambda/2)^2 - L^2(\beta - bi_0/y_0)} . \tag{20}$$

The formula (20) includes all previous non-capacitative velocity formulas as special cases. For example, the Lapicque theory velocity which was shown to be a constant but whose exact value could not be determined (Rashevsky, 1931) is

$$v = (\alpha\lambda L/2) + \sqrt{(\alpha\lambda L/2)^2 + L^2 bi_0/y_0} \tag{21}$$

while the Blair theory velocity, which is essentially the same as the normally accommodated two-factor velocity (Rashevsky, 1938, p. 212), is

$$v = \alpha L \lambda . \tag{22}$$

Since the Blair velocity is zero if the negative sign is used in (20) only the larger positive root is allowed there.

A comparison of (18) and (22) shows immediately that if λ can be assumed to be a physical quantity independent of the circuit considered, the non-capacitative velocity, $v_{non-cap}$, is greater than the capacitative velocity, v_{cap}. An estimate of the difference between them can be made by assuming $\alpha \backsim 1/C\rho$. Then from (18) and (22)

$$v_{non-cap} = \sqrt{1 + \lambda}\ v_{cap}$$

and if $\lambda \backsim 2$, $v_{non-cap} \backsim 1.7 v_{cap}$, so that the non-capacitative velocity is considerably larger than the capacitative.

As has been mentioned already, the method outlined here is sufficiently general to handle any formal conduction theory in a straightforward, simple manner. It seems unlikely however, that formal theories of nerve conduction will ever be able to explain the more intimate characteristics of propagation phenomena; rather, it would appear to the author that further theoretical development ought to be in the line of increasing the physical content of the theory, and, in particular, deducing the formal laws of excitation from structurally plausible, physical postulates.

* As will be seen presently, only the larger root is of interest.

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A NOTE ON THE HOROPTER

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By assuming the fixity (but not the symmetry) of corresponding points on the two retinae, it is possible to derive the equation of any horopter when one is known. In particular when, as experiment shows, one horopter is linear, then all horopters must be conics. These have the form given by Ogle, but whereas Ogle leaves one parameter undetermined at each fixation, on our assumption the only arbitrary parameter is determined by the position of the linear horopter.

It is well known, and easily verified, that when any fixed object, not too far away, is fixated by the two eyes, then near objects as well as distant objects appear double, whereas objects in some region which includes the object fixated do not appear double. That is, when the eyes are held fixed, the two retinal images of any given object will or will not be fused, depending upon its position relative to the observer and to the object he is fixating. Therefore it may be supposed that to each point on one retina there corresponds a unique point on the other retina, called its "corresponding point," which is such that if the same object is imaged on these two corresponding points the two images will fuse. Thus there is established a one-to-one correspondence between the points on the two retinae, and if the optical system of the eye were specified, and the correspondence were known, then, the eyes remaining fixed, one could determine the locus of points in space whose images would fuse, i.e., whose images would fall on corresponding retinal points. This locus would be a piece of an ordinary surface in space, known as the horopter.

Actually it is known that to a given point on one retina there corresponds a region of points on the other retina in the sense that fusion can occur, although the fusion becomes more and more difficult as the region is departed from. Certainly the boundaries of this region are not clearly defined. We may therefore think of each point on one retina as having a unique, "truly" corresponding, point on the other at which fusion is easiest, and that as this point is departed from in any direction the fusion becomes increasingly more difficult and the splitting of the images increasingly easy. We shall therefore continue to speak of retinal correspondence as a one-to-one correspondence. Images of the same object which fall upon points that do not correspond in this sense will (as is customary) be said to be disparate, even

though they may fuse for the observer. Also we may distinguish among nasal or medial disparity, temporal or lateral disparity and vertical disparity, the adjectives being self-explanatory.

Depth perception may be "explained" in terms of the horopter by saying that objects whose images are medially disparate appear farther, those whose images are laterally disparate appear closer, than points on the horopter, this being true whether or not fusion has occurred. This, however, is not a true *explanation,* and for several reasons. First, it says nothing about the subjective form of the horopter and how it is achieved. Second, while we may grant that medially disparate images should be qualitatively different from laterally disparate images, whether or not these are fused, nothing is said about how these qualitative differences become organized into a unified, three-dimensional space with quantitative attributes (Roelofs, 1935). Finally, the manner in which fusion occurs remains a mystery. Nevertheless, the notion of the horopter is a useful descriptive concept in discussions of depth perception.

Let us restrict ourselves in the present discussion to the consideration of the horopter curve, which is the intersection of the horopter surface with the plane of the visual axes. We need to consider then only those light rays which lie in this plane, and this restriction will be tacitly assumed hereafter. Now it is convenient to suppose, first, that the light rays from any point to its retinal image can be represented by a straight line passing through some point in the bulbus — say the nodal point — which is common to all rays, and second, that the position of this point does not vary sensibly with respect to the retina as a result of accommodation. This is equivalent to saying that this common point can be regarded as the center of a pencil of lines through the points of the retina, that each of these lines gives the projection of a point in space upon a retinal point which is the optical image of the space point, and that the Euclidean properties of this pencil as determined by the retinal points are invariant under changes in accommodation, as well as position. Where the image is not in focus on the retina we must regard the line as passing through the center of the circle of confusion on the retina.

We now make a second assumption to the effect that the relation of correspondence, as defined above, is invariant under changes in position and accommodation. Thus if the retinal point P of the left eye corresponds to the retinal point Q of the right eye when the eyes are in one position, they will correspond when the eyes are in any position whatsoever.

One attempt to give a rational derivation and mathematical representation of the horopter curve has resulted in the circles of Vieth

and Müller, and is made on the basis of the further assumption that the eyes are essentially symmetrical, with corresponding rays (lines leading to corresponding points on the two retinae) making equal angles with the visual axes. These circles are therefore coaxal circles — the centers of the pencils being regarded as fixed in space — the common intersections of the circles being the centers of the pencils. Unfortunately, these circles fail to represent adequately the experimental results, for it is found that in all cases the empirical horopter has less curvature toward the observer, and in fact for distant vision the horopter actually has its concavity directed away from the observer. Lying intermediate to the horopters with concavity directed toward, and those with concavity directed away from the observer, there is found to be one which is a straight line (Southall, 1937; Ogle, 1938).

The simplest family of curves possessing the properties here described is evidently a family of conics, and Ogle (1938) has derived the equations of the horopters on the assumption that they are conics passing through the centers of the visual pencils. For horopters which are symmetric with respect to the frontal plane these conics depend upon a single parameter, aside from those which are directly accessible, viz., the distance between the eyes and the location of the fixation point. This parameter, H, would be zero for the Vieth-Müller circles, but empirically it is in general positive. Ogle's derivation does not relate the values of H for different fixations of the same subject.

This note is intended to point out that on the assumptions as to the invariance of the form of the pencils to the retinae and of the relation of correspondence, it is possible, given the horopter curve for one fixation, to predict the form of the curve for any fixation. In particular, from the fact that one horopter curve is linear, it follows easily that the other curves must be conics of the type described. This is true whether or not the linear horopter is perpendicular to the frontal plane.

Let the centers of the pencils at the two eyes be located at $(\pm a, 0)$; let α and $\pi - \alpha$ be the inclinations (in the sense of elementary analytic geometry) of the visual axes for the particular symmetric fixation which yields the linear horopter; let β be the inclination of the linear horopter; let θ_1 and θ_2 be the angles made with the visual axes by a pair of corresponding rays (lines of the pencil passing through corresponding points on the two retinae). The assumption of invariance means simply that the functional relation between θ_1 and θ_2 is independent of the position of the two eyes. Hence, since in this position the two pencils are in perspective (in the sense of projective geometry), the pencils remain projectively related, and therefore the the locus of their intersections is always a conic.

Any ray of the one pencil can be written in the form

$$-x \tan \alpha + (1 + \lambda_1) y - a \tan \alpha = 0 ,$$

and any ray of the other in the form

$$x \tan \alpha + (1 + \lambda_2) y - a \tan \alpha = 0 .$$

The condition that the rays be corresponding is that they intersect on the line

$$x \tan \beta - y + a \tan \alpha = 0 ,$$

and hence that the determinant of the three linear equations shall vanish. This condition is equivalent to the condition

$$\lambda_1 / \sin (\alpha - \beta) = \lambda_2 / \sin (\alpha + \beta) = \nu ,$$

where ν is an auxiliary parameter. Hence we have the equations for corresponding lines in the form

$$\begin{aligned} -x \tan \alpha + [1 + \nu \sin (\alpha - \beta)] y - a \tan \alpha = 0 , \\ x \tan \alpha + [1 - \nu \sin (\alpha + \beta)] y - a \tan \alpha = 0 . \end{aligned} \tag{1}$$

Therefore

$$\begin{aligned} \tan \vartheta_1 &= \frac{-\nu \sin (\alpha - \beta) \tan \alpha}{\sec^2 \alpha + \nu \sin (\alpha - \beta)} , \\ \tan \vartheta_2 &= \frac{-\nu \sin (\alpha + \beta) \tan \alpha}{\sec^2 \alpha - \nu \sin (\alpha + \beta)} . \end{aligned} \tag{2}$$

From this it follows that

$$\sin (\alpha + \beta) \cot \vartheta_2 - \sin (\alpha - \beta) \cot \vartheta_1 = 2 \cos \alpha \cos \beta , \tag{3}$$

which is analogous to Ogle's relation (10). In the special case that $\beta = 0$, this relation becomes

$$\cot \vartheta_2 - \cot \vartheta_1 = 2 \cot \alpha . \tag{4}$$

On the basis of our assumptions, Ogle's parameter H for the symmetric horopter is equal to $2 \cot \alpha$.

Suppose, now, that the left eye is rotated through an angle ω_1, and the right eye through an angle ω_2. For symmetric fixation these angles are equal and opposite. The equation of the corresponding lines are then

$$\tan (\alpha + \theta_1 + \omega_1) \equiv \frac{\tan \alpha + \tan \omega_1 + \nu \sin (\alpha - \beta) \tan \omega_1}{1 - \tan \alpha \tan \omega_1 + \nu \sin (\alpha - \beta)} = \frac{y}{x + a} ,$$

and

$$\tan(\pi-\alpha+\theta_2+\omega_2) \equiv \frac{-\tan\alpha+\tan\omega_2-\nu\sin(\alpha+\beta)\tan\omega_2}{1+\tan\alpha\tan\omega_2-\nu\sin(\alpha+\beta)} = \frac{y}{x-a},$$

or

$$\begin{aligned}(x+a)(\tan\alpha+\tan\omega_1) - (1-\tan\alpha\tan\omega_1)y + \nu\sin(\alpha-\beta)\\ \times[(x+a)\tan\omega_1 - y] = 0,\\ (x-a)(\tan\alpha-\tan\omega_2) + (1+\tan\alpha\tan\omega_2)y + \nu\sin(\alpha+\beta)\\ \times[(x-a)\tan\omega_2 - y] = 0.\end{aligned} \tag{5}$$

By eliminating ν between these two equations we obtain the equation of the locus of intersections of corresponding lines which is the horopter. This can be written in the form

$$\begin{vmatrix}(x+a)\sin(\alpha+\omega_1)-y\cos(\alpha+\omega_1) & [(x+a)\sin\omega_1-y\cos\omega_1]\sin(\alpha-\beta)\\ (x-a)\sin(\alpha-\omega_2)+y\cos(\alpha-\omega_2) & [(x-a)\sin\omega_2-y\cos\omega_2]\sin(\alpha+\beta)\end{vmatrix} = 0. \tag{6}$$

Thus when the linear horopter is known, the horopter corresponding to any other fixation point can be determined.

The horopter is symmetric when and only when the coefficient of xy vanishes in the expansion of (6). This coefficient is found, after some trigonometric transformations, to be

$$\sin 2\alpha\sin(\beta-\omega_1-\omega_2).$$

Hence the horopter is symmetric when

$$\beta-\omega_1-\omega_2 = 0 \tag{7}$$

This is true, in particular, when the fixation is symmetric and $\beta = 0$. In general the locus of fixation points for symmetric horopters is the curve

$$(x^2-y^2-a^2)\tan\beta + 2xy = 0, \tag{8}$$

which is a hyperbola whose center is at the origin and whose transverse axis has the inclination $\pi/4-\beta/2$.

For symmetric convergence at the point $[0, a\tan(\alpha-\omega_1)]$, where $\omega_1 = -\omega_2 = \omega$, the tangent to the horopter at this point is

$$y = (x\tan\beta\cot\alpha - a)\tan(\alpha+\omega),$$

so that the slope here is $\tan\beta\cot\alpha\tan(\alpha-\omega)$. All these tangents pass through the point $(-a\tan\alpha\cot\beta, 0)$, which is the intercept of the linear horopter with the x-axis.

Essentially three assumptions are involved in the derivation of

equation (6). One is the empirical fact that some horopter curve is linear. Another is that accommodative movements can be neglected. Presumably the validity of this assumption can be estimated by a consideration of the optical system of the eye.

The third assumption is to the effect that the relation of correspondence is a fixed relation. This cannot be verified directly, but can only be inferred from theoretical considerations — unless, indeed, histological examinations can reveal the individual fiber pathways to the fusion center, wherever this may be. The theoretical neural mechanism proposed by Verhoeff (1925) seems to imply such a fixity. And if equation (6) is found to agree with experiment, this fact would lend indirect empirical support to the notion.

Actually equation (6) is based upon a further approximation, for it has been made on the assumption that the centers of the pencils of rays were also the centers of rotation of the two eyes. This, of course, is not the case, though the discrepancy would be negligible unless the fixation point is near. The exact equation to replace (6) can be worked out in the same way, but is considerably more complicated.

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THE GENERAL FLUID CIRCUIT THEORY OF ACTIVE CHLORIDE ABSORPTION

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The original fluid circuit theory used to explain active intestinal absorption of chloride is modified to include diffusion and secretion of chloride and osmosis. The general differential equation developed is integrated in a particular case. The definition, "effective concentration of chloride in the fluid passing into the intestinal lumen," leads to simplified general expressions.

In an attempt to explain the absorption of chloride against concentration gradients which occurs in the ileum of the small intestine, R. C. Ingraham, H. C. Peters, and M. B. Visscher (1938, 1939) proposed the "fluid circuit" theory, which assumes that the absorption of water carries chloride out of the intestinal contents without changing its concentration from that in the lumen while a fluid free of chloride moves from the blood into the intestinal lumen. With the additional assumption that the rates of water transfer are constant the theory led to the equations:

$$C/C_0 = (V/V_0)^{R_i/D} \tag{1}$$

and

$$V = V_0 - Dt\,, \tag{2}$$

where C and V are concentration and volume at time t, C_0 and V_0 their initial values, R_i the rate of movement of fluid into the intestinal lumen, and D the rate of volume decrease.

Concentration time curves for chloride absorption from a solution containing half isotonic sodium chloride and half isotonic sodium sulfate agreed satisfactorily with the theory except at low chloride concentrations. Since secretion and diffusion of chloride and osmosis have been neglected in the derivation of equations (1) and (2), it seemed desirable to develop the theory on a more general basis. This has been done as follows. We have

$$I = CV\,, \tag{3}$$

where I is the amount of chloride present in the intestinal lumen.

$$dI/dt = C(dV/dt) + V(dC/dt)\,. \tag{4}$$

$$dI/dt = C_s S + K(C_p - C) - CR_0 , \tag{5}$$

where S is the rate of secretion of a fluid having a chloride concentration C_s, K a coefficient, C_p the plasma chloride concentration, and R_0 the rate of fluid movement out of the intestinal lumen.

From equations (4) and (5),

$$C(dV/dt) + V(dC/dt) = C_s S + K(C_p - C) - CR_0 . \tag{6}$$

This is the equation for the general fluid circuit theory. It can be easily integrated, in the particular case in which dV/dt, C_s, S, K, C_p, and R_0 are constants, as follows:

If $dV/dt = -D$, then, from equation (6),

$$\frac{dC}{dt} = \frac{C_s S + K(C_p - C) - CR_0 + DC}{V} . \tag{7}$$

Substituting $dV/-D$ for dt and rearranging,

$$\frac{dC}{(R_0 + K - D)C - C_s S - KC_p} = \frac{dV}{DV} . \tag{8}$$

Integrating between the limits C_0 and C, and V_0 and V,

$$\frac{(R_0 + K - D)C - C_s S - KC_p}{(R_0 + K - D)C_0 - C_s S - KC_p} = \left(\frac{V}{V_0}\right)^{(R_0+K-D)/D} , \tag{9}$$

where V is given by equation (2).

Equations (9) and (2) will fit the data of Ingraham et al. satisfactorily at low chloride concentrations. At the present time however its use appears to be limited to relatively short experiments under restricted conditions.

Equation (6) may be simplified by using the definition

$$C_e = [C_s S + K(C_p - C)]/R_i , \tag{10}$$

where C_e is the effective concentration of chloride in the fluid passing into the intestinal lumen at rate R_i. R_i includes osmotic as well as secretory water transfer. Substituting in equation (6),

$$C(dV/dt) + V(dC/dt) = C_e R_i - CR_0 . \tag{11}$$

At any instant

$$dV/dt = R_i - R_0 - R_{0s} , \tag{12}$$

where R_{0s} is the rate of water transfer by osmosis in the direction intestine to blood only. If osmosis is in the opposite direction it is included in R_i.

From equations (11) and (12),

$$V(dC/dt) = C_e R_i - C(R_i - R_{0s}) . \qquad (13)$$

If $dC/dt = 0$, then $C_e = C(R_i - R_{0s})/R_i$ and $C_e \leqq C$.

Similarly if $dC/dt < 0$, then $C_e < C$; and if $dC/dt > 0$, then $C_e > C(R_i - R_{0s})/R_i$.

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